General

Guideline Title

Venous thromboembolism prophylaxis in hospitalized patients: a clinical practice guideline from the American College of Physicians.

Bibliographic Source(s)

Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P, for the Clinical Guidelines Committee of the American College of Physicians. Venous thromboembolism prophylaxis in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2011 Nov 1;155(9):625-32. [50 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the strength of evidence (high, moderate, low, or insufficient evidence to determine net benefits or risks) and strength of recommendations (strong, weak) are defined at the end of the "Major Recommendations" field.

Recommendations

Recommendation 1: *The American College of Physicians (ACP) recommends assessment of the risk for thromboembolism and bleeding in medical (including stroke) patients prior to initiation of prophylaxis of venous thromboembolism (VTE)* (Grade: strong recommendation, moderate-quality evidence).

The decision to initiate VTE prophylaxis in medical (including stroke) patients should be based on an individualized assessment of the risk for thromboembolism and bleeding, as well as an assessment of the potential harms against modest or even no benefit. Trials that evaluated the benefits and harms of heparin prophylaxis generally enrolled patients who were considered to be at higher risk for VTE. Risk factors for thromboembolism include presence of inherited conditions—such as factor V Leiden mutation, prothrombin gene mutation, protein S or C deficiency, and antithrombin deficiency—or acquired risk factors—such as surgery, cancer, immobilization, trauma, presence of a central venous catheter, pregnancy, drugs (for example, oral contraceptives, hormone replacement therapy, or tamoxifen), congestive heart failure, chronic renal disease, the antiphospholipid antibody syndrome, obesity, smoking, older age, and history of thromboembolism. Some evidence suggests that heparin is less beneficial in younger patients than in patients older than 75 years. Many risk assessment tools are available for estimating thromboembolism risk, but the current evidence is insufficient to recommend a validated tool. Although such instruments may be useful, decisions about heparin prophylaxis may also be based on general evidence regarding the risk factors for VTE and bleeding.

Heparin and related drugs are associated with an increased risk for bleeding. Risk factors for bleeding with anticoagulant therapy include older age;

female sex; diabetes; hypertension; presence of cancer; acute or chronic alcoholism; liver disease; severe chronic kidney disease; peptic ulcer disease; anemia; poor treatment adherence; prior stroke or intracerebral hemorrhage; presence of bleeding lesions; bleeding disorder; and concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, antiplatelet agents, antibiotics, statins, fibrates, and steroids.

Recommendation 2: *ACP recommends pharmacologic prophylaxis with heparin or a related drug for VTE in medical (including stroke) patients unless the assessed risk for bleeding outweighs the likely benefits* (Grade: strong recommendation, moderate-quality evidence).

In hospitalized medical patients, prophylaxis with heparin is associated with a statistically significant reduction in pulmonary embolisms (PEs) (absolute decrease, 4 events per 1000 persons treated) and increase in all bleeding events (absolute increase, 9 events per 1000 persons treated), a non–statistically significant increase in major bleeding events (absolute increase, 1 event per 1000 persons treated), and no effect on mortality or symptomatic deep venous thrombosis (DVT). In most patients, the clinical benefit of reduction of PEs outweighs the harm of increased risk for bleeding events.

In patients with acute stroke, the pooled results from the evidence review showed no statistically significant benefit from heparin prophylaxis on mortality, PE, or symptomatic DVT. The pooled results also showed a statistically significant increase in risk for major bleeding events (absolute increase, 6 events per 1000 persons treated) that outweighed the potential reduction in PEs (absolute decrease, 3 events per 1000 persons treated). However, the pooled results showed wide confidence intervals (CIs) that also encompassed potential substantial net benefits. Seven of 8 studies that evaluated the effect of heparin on mortality were small (sample size range, 32 to 305 participants) and were published before 1996. Some did not describe use of CT to exclude intracranial hemorrhage before randomization. The strongest evidence in patients with stroke comes from the International Stroke Trial, a large study that randomly assigned 14,578 patients with suspected acute ischemic stroke to receive low-dose (5000 IU twice daily) heparin or no heparin. It found no statistically significant differences between low-dose heparin and no heparin in 14-day all-cause mortality, fatal PE, or all (fatal and nonfatal) PEs. Although the risk for hemorrhagic stroke or serious extracranial hemorrhage statistically significantly increased (absolute increase, 5 events per 1000 persons treated), this was offset by a statistically significant and larger decrease in risk for recurrent ischemic stroke (absolute decrease, 14 events per 1000 persons treated). Results of the International Stroke Trial and pooled estimates from patients with stroke were generally consistent with findings from pooled analyses of medical patients without stroke; thus, evidence was insufficient to conclude that risks and benefits of VTE prophylaxis differ between medical patients with stroke and those without stroke. Evidence on the risks and benefits in patients with stroke is relatively weaker than that in medical patients without stroke, although prevention of recurrent ischemic stroke may be an additional benefit in this population.

The optimal duration of heparin prophylaxis is uncertain. Almost all trials evaluated heparin therapy for patients during hospitalization. A recent study evaluated extended (posthospitalization) heparin therapy for high-risk (immobile) patients, but more research is needed to understand the effects of extended therapy on the balance of benefits and harms.

Clinical benefits and harms do not statistically significantly differ between low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH). Fondaparinux has not been directly compared with heparin. All prophylactic heparins reviewed for this guideline are administered as subcutaneous injections. The dosage varies from 2 or 3 times daily for UFH to once daily for LMWH or fondaparinux. The average wholesale drug costs are about $10 per day for UFH, $35 per day for LMWH (generic enoxaparin is available), and $60 per day for fondaparinux. In 4 trials that compared UFH with LMWH and assessed heparin-induced thrombocytopenia, 7 cases of heparin-induced thrombocytopenia occurred out of about 1900 in patients receiving UFH and 1 case occurred out of about 1900 patients receiving LMWH (P=0.07). Hence, the choice of agent for prophylaxis of VTE should be based on ease of use, adverse effect profile, and cost of medication.

Recommendation 3: *ACP recommends against the use of mechanical prophylaxis with graduated compression stockings for prevention of VTE* (Grade: strong recommendation, moderate-quality evidence).

Mechanical prophylaxis with graduated compression stockings was not effective in preventing VTE or reducing mortality and resulted in clinically important lower-extremity skin damage. Clinicians who initiate VTE prophylaxis should select heparin (or related drugs) rather than graduated compression stockings for patients in whom heparin can be used. In patients at high risk for bleeding events or in whom heparin is contraindicated for other reasons, intermittent pneumatic compression may be a reasonable option, because evidence suggests that it is beneficial in surgical patients. However, intermittent pneumatic compression has not been sufficiently evaluated as a stand-alone intervention in medical patients to reliably estimate benefits and harms.

See the Figure in the original guideline document for a summary of the recommendations and clinical considerations.

Policy Implication

ACP does not support the application of performance measures in medical (including stroke) patients that promotes universal VTE prophylaxis regardless of risk.

In the United States, many organizations have developed performance measures intended to increase the appropriate use of VTE prophylaxis in hospitalized patients. However, in some clinical settings, performance measures have been based on rates of VTE prophylaxis in all patients, regardless of their underlying risk. The evidence reviewed for the clinical recommendations in this guideline does not support routine prophylaxis of VTE in all medical patients and emphasizes the tradeoff in harms and benefits. Clinicians caring for these patients must assess the risks and benefits before deciding whether to initiate prophylaxis. In some cases, not prescribing VTE prophylaxis may be justified because the estimated trade-off between potential risks and benefits is small or unclear. Because no standard, accepted formula for risk assessment exists to identify which medical patients are likely to benefit from VTE prophylaxis, the decision is best left to physician judgment, and performance measures targeting all patients are inappropriate. Until physicians can better identify patients who truly benefit, performance measures that encourage VTE prophylaxis for all medical patients may encourage physicians to use prophylaxis in low-risk patients for whom the risks may exceed the benefit.

Definitions:

The American College of Physicians' Guideline Grading System*		
Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced with Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

*Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Venous thromboembolism, including:

- Pulmonary embolism (PE)
- Deep venous thrombosis (DVT)

Guideline Category

Assessment of Therapeutic Effectiveness

Prevention

Risk Assessment

Clinical Specialty

Cardiology

Critical Care

Family Practice

Geriatrics

Hematology

Internal Medicine

Neurology

Preventive Medicine

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Hospitals

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To present clinical recommendations on prophylaxis of venous thromboembolism (VTE) in adult hospitalized medical patients and patients with acute stroke, based on the available evidence on the benefits and harms of prophylaxis of VTE in these patient populations

Target Population

Adult hospitalized nonsurgical patients (medical patients and patients with acute stroke) who are at risk for venous thromboembolism

Interventions and Practices Considered

1. Assessment of the risk for thromboembolism and bleeding prior to initiation of prophylaxis of venous thromboembolism
2. Venous thromboembolism prophylaxis:
    - Low-dose low-molecular-weight heparin (LMWH)
    - Low-dose unfractionated heparin (UFH)
    - Related agents (e.g., fondaparinux)
    - Graduated compression stockings or other mechanical compression (not recommended)

Major Outcomes Considered

- Total mortality up to 120 days after randomization
- Incidence of symptomatic deep venous thrombosis (DVT)
- Total incidence of pulmonary embolisms (PEs)
- Incidence of fatal PE
- Incidence of all bleeding events
- Incidence of major bleeding events (variably defined by trials, but typically defined as a decrease in hemoglobin level >20 g/L, transfusion of

≥2 units of blood, or life-threatening bleeding at a critical site)
- Effects of mechanical prophylaxis on skin

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The systematic evidence review was conducted by the Minnesota Evidence-based Practice Center (see the "Availability of Companion Documents" field). The literature search included studies identified by using MEDLINE and the Cochrane Library for clinical trials of venous thromboembolism (VTE) prophylaxis. The authors reviewed titles and abstracts of identified references and used reference lists of pertinent randomized trials and systematic reviews to identify additional reports. The studies selected included English-language, randomized trials published between 1950 and April 2011. Included trials evaluated treatments that are commonly recommended and used to prevent VTE, including subcutaneous low-dose (<20 000 U/d) unfractionated heparin (UFH) or similar prophylactic doses of low-molecular-weight heparin (LMWH) or related agents (such as fondaparinux) and graduated compression stockings or other mechanical measures (such as intermittent pneumatic compression).

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

This guideline rates the evidence and recommendations by using the guideline grading system of the American College of Physicians (ACP), which is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (see the "Rating Scheme for the Strength of the Recommendations" field).

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

To guide the recommendations, the authors prioritized outcomes on the basis of clinical importance, starting with total mortality. In the absence of statistically significant effects on total mortality, the authors then weighted effects on all pulmonary embolisms (PEs) versus effects on major bleeding events, followed by symptomatic deep venous thrombosis (DVT), all bleeding (including minor bleeding) events, and effects of mechanical prophylaxis on skin.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline is based on a systematic evidence review that addressed the following questions:

- Key question 1: What are the benefits and harms of subcutaneous low-dose heparin products for venous thromboembolism (VTE) prophylaxis in hospitalized medical patients?
- Key question 2: What is the comparative effectiveness of different low-dose heparin products (low-molecular-weight heparin [LMWH], unfractionated heparin [UFH]) for VTE prophylaxis?
- Key question 3: What is the effectiveness and comparative effectiveness of mechanical devices for VTE prophylaxis?
- Key question 4: Do results vary by general medical patient populations: general medical inpatients and patients with acute stroke?

Rating Scheme for the Strength of the Recommendations

The American College of Physicians' Guideline Grading System*		
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	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced with Risks and Burden
High	Strong	Weak
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Insufficient evidence to determine net benefits or risks		

*Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was approved by the American College of Physicians (ACP) Board of Regents on 30 July 2011. The ACP Performance Measurement Committee also reviewed and commented on the manuscript.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Treatment benefits for venous thromboembolism (VTE) are primarily related to reduction in mortality, symptomatic deep venous thrombosis (DVT), and pulmonary embolism (PE) events.

Potential Harms

Heparin and related drugs are associated with an increased risk for bleeding. Risk factors for bleeding with anticoagulant therapy include older age; female sex; diabetes; hypertension; presence of cancer; acute or chronic alcoholism; liver disease; severe chronic kidney disease; peptic ulcer disease; anemia; poor treatment adherence; prior stroke or intracerebral hemorrhage; presence of bleeding lesions; bleeding disorder; and concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, antiplatelet agents, antibiotics, statins, fibrates, and steroids.

Qualifying Statements

Qualifying Statements

- Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All American College of Physicians (ACP) clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.
- The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the U.S Department of Veterans Affairs.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Mobile Device Resources

Patient Resources

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Nov 1

Guideline Developer(s)

American College of Physicians - Medical Specialty Society

Source(s) of Funding

American College of Physicians

Guideline Committee

Clinical Guidelines Committee of the American College of Physicians

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Financial Disclosures/Conflicts of Interest

Any financial and nonfinancial conflicts of interest of the group members were declared, discussed, and resolved. Dr. Humphrey: Consultancy: U.S. Preventive Services Task Force. Royalties: Up-To-Date. Dr. Shekelle: Consultancy: ECRI Institute; Employment: Department of Veterans Affairs; Grants/grants pending (money to institution): Agency for Healthcare Research and Quality, Department of Veterans Affairs, Centers for Medicare & Medicaid Services; Royalties: Up-To-Date. Disclosures can also be viewed at https://www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-1931.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Annals of Internal Medicine Web site.

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

Availability of Companion Documents

The following are available:

- Qaseem A, Snow V, Owens DK, Shekelle P. The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. Ann Intern Med. 2010 Aug 3;153(3):194-199. Electronic copies: Available from the Annals of Internal Medicine Web site.
- Lederle FA, Zylla D, MacDonald R, Wilt T. Venous thromboembolism prophylaxis in hospitalized medical patients and those with stroke: background review for an American College of Physicians clinical practice guideline. Ann Intern Med. 2011;155:602-615. Electronic copies: Available from the Annals of Internal Medicine Web site.

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

A collection of Recommendation Summaries for all current American College of Physicians (ACP) Clinical Guidelines is now available for mobile devices from the ACP Web site.

A continuing medical education (CME) course is also available from the Annals of Internal Medicine Web site.

Patient Resources

The following is available:

- Summaries for patients. Preventing venous thromboembolism in hospitalized patients: Recommendations from the American College of Physicians. Ann Intern Med. 2011 Nov 1;155(9):I-38. Electronic copies: Available from the Annals of Internal Medicine Web site.

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

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NGC Status

This NGC summary was completed by ECRI Institute on December 2, 2011. This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

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